AMENDMENT OF SOLICITATION/MODIFICATION OF CONTRACT

1. CONTRACT ID CODE	PAGE OF PAGES
	1 2

2. AMENDMENT/MODIFICATION NO.	3. EFFECTIVE DATE	4. REQUISITION/PURCHASE REQ. NO.	5. PROJECT NO. *(If applicable)*
P00002	See Block 16C		

6. ISSUED BY	CODE	7. ADMINISTERED BY *(If other than Item 6)*	CODE
CAD	CAD		

CAD
US Environmental Protection Agency
26 West Martin Luther King Drive
Mail Code: W136
Cincinnati OH 45268-0001

8. NAME AND ADDRESS OF CONTRACTOR *(No., street, county, State and ZIP Code)*

National Academy of Sciences
Attn: JAMES BURKE
500 FIFTH STREET NW
WASHINGTON DC 200012736

CODE 041964057 FACILITY CODE

(x) 9A. AMENDMENT OF SOLICITATION NO.

9B. DATED *(SEE ITEM 11)*

X 10A. MODIFICATION OF CONTRACT/ORDER NO.
68HERC19D0011
68HERC21F0178

10B. DATED *(SEE ITEM 13)*
03/23/2021

11. THIS ITEM ONLY APPLIES TO AMENDMENTS OF SOLICITATIONS

☐ The above numbered solicitation is amended as set forth in Item 14. The hour and date specified for receipt of Offers ☐ is extended. ☐ is not extended.
Offers must acknowledge receipt of this amendment prior to the hour and date specified in the solicitation or as amended , by one of the following methods: (a) By completing Items 8 and 15, and returning _____ copies of the amendment; (b) By acknowledging receipt of this amendment on each copy of the offer submitted ; or (c) By separate letter or electronic communication which includes a reference to the solicitation and amendment numbers. FAILURE OF YOUR ACKNOWLEDGEMENT TO BE RECEIVED AT THE PLACE DESIGNATED FOR THE RECEIPT OF OFFERS PRIOR TO THE HOUR AND DATE SPECIFIED MAY RESULT IN REJECTION OF YOUR OFFER. If by virtue of this amendment you desire to change an offer already submitted , such change may be made by letter or electronic communication, provided each letter or electronic communication makes reference to the solicitation and this amendment, and is received prior to the opening hour and date specified.

12. ACCOUNTING AND APPROPRIATION DATA *(If required)*
See Schedule

13. THIS ITEM ONLY APPLIES TO MODIFICATION OF CONTRACTS/ORDERS. IT MODIFIES THE CONTRACT/ORDER NO. AS DESCRIBED IN ITEM 14.

CHECK ONE	
	A. THIS CHANGE ORDER IS ISSUED PURSUANT TO: *(Specify authority)* THE CHANGES SET FORTH IN ITEM 14 ARE MADE IN THE CONTRACT ORDER NO. IN ITEM 10A.
	B. THE ABOVE NUMBERED CONTRACT/ORDER IS MODIFIED TO REFLECT THE ADMINISTRATIVE CHANGES *(such as changes in paying office, appropriation data, etc.)* SET FORTH IN ITEM 14, PURSUANT TO THE AUTHORITY OF FAR 43.103(b).
	C. THIS SUPPLEMENTAL AGREEMENT IS ENTERED INTO PURSUANT TO AUTHORITY OF:
	D. OTHER *(Specify type of modification and authority)*

E. IMPORTANT: Contractor ☒ is not ☐ is required to sign this document and return _____ copies to the issuing office.

14. DESCRIPTION OF AMENDMENT/MODIFICATION *(Organized by UCF section headings, including solicitation/contract subject matter where feasible.)*

DUNS Number: 041964057
TOCOR: KAI THOMPSON Max Expire Date: 03/22/2023
LIST OF CHANGES:
Reason for Modification: The purpose of this modification will be to execute the revised PWS for this no cost change.

Continued ...

Except as provided herein, all terms and conditions of the document referenced in Item 9 A or 10A, as heretofore changed, remains unchanged and in full force and effect.

15A. NAME AND TITLE OF SIGNER *(Type or print)*		16A. NAME AND TITLE OF CONTRACTING OFFICER *(Type or print)*	
		William M. Yates	
15B. CONTRACTOR/OFFEROR	15C. DATE SIGNED	16B. UNITED STATES OF AMERICA	16C. DATE SIGNED
(Signature of person authorized to sign)		William Yates ELECTRONIC SIGNATURE *(Signature of Contracting Officer)*	09/28/2021

NAME OF OFFEROR OR CONTRACTOR
National Academy of Sciences

ITEM NO. (A)	SUPPLIES/SERVICES (B)	QUANTITY (C)	UNIT (D)	UNIT PRICE (E)	AMOUNT (F)
	Payment: RTP Finance Center US Environmental Protection Agency RTP-Finance Center (AA216-01) 109 TW Alexander Drive www2.epa.gov/financial/contracts Durham NC 27711 Period of Performance: 03/23/2021 to 03/21/2023				

THE NATIONAL ACADEMIES OF SCIENCES, ENGINEERING, AND MEDICINE
DIVISION ON EARTH AND LIFE STUDIES
BOARD ON ENVIRONMENTAL STUDIES AND TOXICOLOGY
INSTITUTE FOR LABORATORY ANIMAL RESEARCH

PROPOSAL NO: 10005365

VARIABILITY AND RELEVANCE OF CURRENT LABORATORY MAMMALIAN TOXICITY TESTS AND EXPECTATIONS FOR NEW APPROACH METHODS (NAMS) FOR USE IN HUMAN HEALTH RISK ASSESSMENT

SUMMARY

The National Academies of Sciences, Engineering, and Medicine (National Academies) propose to assist the U.S. Environmental Protection Agency (EPA) by reviewing the variability and relevance of existing laboratory mammalian toxicity tests for human health risk assessment to inform the development of approaches for validation and establishing scientific confidence in using New Approach Methods (NAMs), and recommendations on expectations associated with NAMs when they cannot be compared with human studies.

The total of $990,257 is requested from the EPA for full support of this study. The work will be conducted collaboratively under the auspices of the National Academies Division on Earth and Life Studies Board on Environmental Studies and Toxicology (BEST) and Institute for Laboratory Animal Research (ILAR).

BACKGROUND

In 2017, the National Academies released a report entitled "Using 21st Century Science to Improve Risk-Related Evaluations." The risk-related applications report highlighted both the progress that had occurred in toxicology and exposure sciences since the release of previous reports and identified several decision contexts that could benefit from application of the advances in the fields. It proposed a shift in thinking of the risk assessment community from whether a chemical causes a particular effect to whether a chemical increases the risk of a particular effect, while also recognizing that one does not need to know all the pathways or components involved in a particular disease to begin applying the new tools to regulatory decisions. The National Academies Committee on Incorporating 21st Century Science into Risk-Based Evaluations also touched on the subject of validation and that many of the traditional processes for validation cannot match the pace of development of new assays, models, and test systems. The report recognized the challenges in validating a NAM where there is no "gold standard" or against toxicity tests that have not themselves been validated. The National Academies Committee highlighted that there were two important issues on which there was still no consensus in the scientific community: 1) evaluation of the validity of assays that are not intended as one-to-one replacements for in vivo toxicity assays; and 2) assessment of the concordance of data from assays that use cells or proteins of human origin with toxicity data that are virtually all derived from animal models.

One of the important considerations in the evaluation of 'equivalent or better' approaches is that laboratory mammalian toxicity data provide a part of the foundation of the current risk assessment paradigm, and mammalian studies often provide the only available in vivo data for many environmental chemicals. There are a number of new evaluations of the qualitative and quantitative variability (Kleinstreuer et al., 2016; Browne et al., 2018; Pham et al., 2020) and human relevance (e.g., Monticello et al., 2017; Hoffmann et al., 2018; Ackley et al., 2019), of laboratory mammalian toxicity studies. These new studies highlight some of the limitations and challenges associated with using laboratory mammalian toxicity data as the standard benchmark for evaluating and implementing NAMs. Since the 2017 National Academies report on 21st Century risk-related evaluations, the state of the science has continued to progress and the understanding and experience with NAMs has led to new considerations and more focused scientific questions. EPA is soliciting support from the National Academies to explore the strengths and limitations of using laboratory mammalian toxicology data as the benchmark for developing and evaluating NAMs, as well as possible novel approaches to validation and confidence building in using NAMs to replace mammalian toxicology data. This scientific exploration will become important in the policy decisions that EPA needs to address with "validation to ensure that NAMs are equivalent to or better than the animal tests replaced."

STATEMENT OF TASK

An ad hoc committee of the National Academies of Sciences, Engineering, and Medicine will provide EPA with a review of the variability and relevance of existing laboratory mammalian toxicity tests for human health risk assessment to inform the development of approaches for validation and establishing scientific confidence in using New Approach Methods (NAMs), and recommendations on expectations associated with NAMs when they cannot be compared with human studies. The work of the study committee will be informed by two public workshops, by a literature review that addresses the variability and human relevance of current laboratory mammalian toxicity tests and approaches to validation and establishing scientific confidence in using NAMs, and by other public information gathering meetings organized by the study committee as needed.

The proposed charge questions are as follows:

1. Does the committee assess the literature review and data provided as reflecting a comprehensive, workable, objective, and transparent process?

2. Given the results of the literature review and workshops, what are the implications of the qualitative and quantitative variability of laboratory mammalian toxicity studies when using them to establish the performance of NAMs?

3. What do the literature review and workshops indicate about concordance between laboratory mammalian models and humans in the adverse effects following chemical exposure and how might this frame expectations of NAMs when they cannot be compared directly with human studies?

4. The Committee shall impart expert advice on addressing the two related issues that were left unresolved in the 2017 NRC report:

a. Evaluation of the validity of assays that are not intended as one-to-one replacements for in vivo toxicity assays; and

b. Assessment of the concordance of data from assays that use cells or proteins of human origin with toxicity data that are virtually all derived from animal models.

5. Based on the conclusions from 1 - 4 above, how may the Committee foresee this information being incorporated into a new or the existing validation paradigm or scientific confidence framework so that EPA can ensure that NAMs are equivalent to or better than the animal tests replaced?

WORK PLAN

Task 1: Establish Public Workshops

An ad hoc committee of the National Academies of Sciences, Engineering, and Medicine will organize two public workshops. The committee will be formed as described in Task 2, Convene Expert Committee. The first workshop will focus on strengths and limitations of using laboratory animal toxicology data as the benchmark for developing and evaluating NAMs. The intent of the first workshop is to ensure a more consistent understanding of the issues and current scientific knowledge across the scientific and stakeholder communities. The workshop will address key science topics including, but not limited to, qualitative and quantitative variability in laboratory mammalian toxicity tests, overall concordance of adverse effects between laboratory mammalian models and humans following exposure to commercial, environmental, and pharmaceutical chemicals, frameworks for validation and establishing scientific confidence, and issues with validation of NAMs that are not intended as one-to-one replacements for laboratory mammalian toxicity studies.

The second workshop will provide input to the committee in support of the consensus report development.

Subtask 1.1 – Initial meeting: National Academies staff will meet with the EPA to review the topics and issues to be discussed at the workshop(s). EPA will identify the topics and review issues via email anticipated to be discussed for each workshop approximately three to six months before the workshop. If necessary, EPA will provide a one-pager with the necessary background information. This preliminary meeting will occur within seven days of EPA identifying the topics and anticipated issues.

Subtask 1.2 – Establish a workshop agenda and a list of participants: The National Academies will convene up to 15 experts, in addition to the committee, to participate in the workshop. National Academies staff will identify and contact non-federal and federal subject matter experts who are (a) recognized experts in the field(s) and issues relevant to the workshop, (b) represent a range of recognized views on the issues identified by EPA, and (c) are available to present and discuss their research and individual views at the public workshop. Experts with an understanding of regulatory risk assessment (e.g., chemical hazards) are generally preferred. National Academies staff will provide the EPA TOCOR a proposed list of experts including a biographical sketch and area of expertise for each expert. The National Academies staff will convene a meeting with the

EPA TOCOR and ORD management and technical staff to review the proposed list of experts. EPA may provide comments on the proposed list regarding qualifications and COI/impartiality. The National Academies staff will determine who will participate in the workshop.

Subtask 1.3. – Conduct the workshop: The National Academies will convene and facilitate the workshop to discuss topics and/or issues pertinent to assessment development. In coordination with the National Academies staff, EPA will provide a general description of the desired goals and outcomes of the workshop. National Academies staff will provide EPA with a list of all registrants and participants after the workshop via email.

The study committee will plan the workshop(s) via conference calls and web-based meetings. The National Academies will provide EPA with a list of all registrants and participants after the workshop(s) via email.

Subtask 1.4. – Make arrangements for logistical support for each expert asked to participate in the workshop: National Academies staff will arrange provision for logistical support for the experts' participation in the workshop, which will be held virtually.

Subtask 1.5 – Develop workshop outputs: Following the first workshop, a designated rapporteur will prepare a proceedings-in-brief in accordance with institutional guidelines. The proceedings-in-brief will summarize the workshop but will not provide consensus findings and recommendations. The proceedings will be subject to appropriate institutional review procedures prior to release and will then be posted to the National Academies' website. The second workshop will not result in a proceedings-in-brief, but the study committee will consider its presentations and discussions in preparing the consensus report, described below in Task 3.

Task 1 Deliverables

a) National Academies staff will inform the TOCOR via email of the time, location, and agenda of the workshop(s) at least 45 days prior to the workshop. The National Academies staff will provide EPA with a final list of all workshop attendees and public commenters within five business days of the workshop.
b) Arrangement and provision of logistical support for the experts' participation in the workshop.
c) National Academies Staff will notify the TOCOR of the location of the website to be used to disseminate information to the public.
d) Proceedings-in-brief report for the first workshop.
e) The workshop(s) will be recorded and the recordings made available on a public website. In addition, transcripts will be made available to EPA and the committee.

Task 2: Convene Expert Committee

Subtask 2.1 – Perform literature review: The National Academies will prepare a review of published literature pertaining to the variability and human relevance of current laboratory mammalian toxicity tests and approaches to validation and establishing

scientific confidence in using NAMs. The literature review will include a protocol, developed with guidance from National Academies staff, describing the databases searched, search terms used, and inclusion and exclusion criteria for the articles. The variability and relevance of the existing laboratory mammalian toxicity tests will be considered by the Committee in terms of reliability, qualitative and quantitative reproducibility as well as biological relevance and overall concordance of the results in humans in the context of toxicity testing and risk assessment. The components of the review will consist of the following:

1. **Variability and Human Relevance of Existing Laboratory Mammalian Toxicity Tests**
   - Qualitative and quantitative variability in laboratory mammalian toxicity tests.
   - Overall concordance between laboratory mammalian models and humans in the adverse effects following exposure to commercial, environmental, and pharmaceutical chemicals, where available.
2. **Frameworks for Validation and Establishing Scientific Confidence**
   - Validation of laboratory mammalian toxicity tests.
   - Frameworks for establishing scientific confidence in NAMs.
   - Identification and description of the issues in the validation of NAMs as a replacement for existing laboratory mammalian toxicity tests.
   - Identification and description of the issues in the validation of NAMs that use cells or proteins of human origin in comparison to laboratory mammalian toxicity data.
   - Identification and description of the issues in the validation of NAMs that are not intended as one-to-one replacements for laboratory mammalian toxicity studies.
3. **Identification of Research Needs**
   - Determination of information gaps in the areas listed above to identify research priorities that could better inform these recommendations.

Subtask 2.2 – Recruit experts: The National Academies will identify and convene an ad hoc committee of no more than sixteen (16) recognized experts each with expertise in one or more of the fields relevant to the study including: in vitro assay and model systems toxicology; human health risk assessment; biostatistics; and veterinary medicine. The EPA may offer suggestions of potential committee members to be considered by the National Academies during its nominations process. EPA may also comment on the proposed committee membership during the 20-day comment period. The National Academies will select the committee members.

Nominations for committee membership will be sought from a broad range of sources, including academia, non-governmental/public interest organizations, private industry, and federal, state, tribal, and local governments. Membership in the NAS, NAE, or NAM and previous involvement in National Academies studies are taken into account in committee selection. The inclusion of women, minorities, and early- to mid-career professionals and geographic diversity are additional considerations. The committee will be formed in accordance with the National Academies policies concerning conflict of interest and bias to ensure a balanced and objective study.

Subtask 2.3 – Post-Recruitment Notification: The National Academies will provide the TOCOR with the proposed list of committee members, including a biographical sketch and proposed area of expertise for each member. EPA may comment on potential committee members as described in Subtask 2.2. For the workshops, the National Academies will determine who will participate in each workshop and will deliver a final list of participants to EPA.

Subtask 2.4 – Expert logistic support: National Academies staff will arrange provision for logistical support for the experts' participation in the workshops, at least one of which will be held virtually. National Academies staff will arrange provision for transportation, lodging, and any other logistical support for additional committee meetings if held in-person.

Task 2 Deliverables

(a) The literature review will be provided to the consensus study committee as input to its deliberations and be made available to EPA and the public as an appendix to the report.
(b) The National Academies will provide EPA with proposed and final lists of experts, including biographical sketches, who will participate in the two workshop(s) specified by EPA. The first workshop will result in a proceedings-in-brief that will summarize the workshop discussions and will be published by the National Academies. The second workshop will not result in a proceedings-in-brief, but the study committee will consider its presentations and discussions in preparing the consensus report, described below in Task 3.

Task 3: Write Report

The ad hoc committee will develop findings and recommendations in a consensus report addressing the statement of task. The committee will consider the results of the workshops and literature review in its deliberations.

As noted previously, the proposed charge questions are as follows:

1. Does the committee assess the literature review and data provided as reflecting a comprehensive, workable, objective, and transparent process?

2. Given the results of the literature review and workshops, what are the implications of the qualitative and quantitative variability of laboratory mammalian toxicity studies when using them to establish the performance of NAMs?

3. What do the literature review and workshops indicate about overall concordance in adverse effects between laboratory mammalian models and humans following chemical exposure and how might this frame expectations of NAMs when they cannot be compared directly with human studies?

4. The committee will impart expert advice on addressing the two related issues that were left unresolved in the 2017 NRC report:
   a. Evaluation of the validity of assays that are not intended as one-to-one replacements for in vivo toxicity assays; and

b. Assessment of the concordance of data from assays that use cells or proteins of human origin with toxicity data that are virtually all derived from animal models.

5. Based on the conclusions from 1 – 4 above, how may the committee foresee this information being incorporated into a new or the existing validation paradigm or scientific confidence framework so that EPA can ensure that NAMs are equivalent to or better than the animal tests replaced?

Subtask 3.1 – Conduct an independent peer review: The committee's draft report will be reviewed in accordance with National Academies' policies and procedures.

Subtask 3.2 – Deliver final report: A prepublication report will be released 20 months after project initiation, and a final will be published within four months of releasing the prepublication. Briefings will be provided to EPA and interested members of Congress. The report will be made available on the National Academies website; other dissemination activities (e.g., briefings and webinars) will be planned in consultation with EPA to ensure that the report results are widely disseminated.

Subtask 3.3. – Conduct additional meetings as necessary: The National Academies may conduct up to three additional virtual public information-gathering sessions that the committee may deem necessary to fill in gaps from the workshop and the literature review as needed. The committee also will meet in closed, deliberative sessions to discuss and write their report.

Task 3 Deliverables

a) National Academies staff will notify the TOCOR of the location of the website to be used to disseminate information to the public (Subtask 3.2).

b) The report detailing the committee's findings will be provided to EPA and made available to the public on the National Academies website.

Task 4: Monthly Progress Reports to TOCOR

National Academies staff will write and submit monthly progress reports to the TOCOR. Progress reports will describe completed work during the invoice period and should link to charges described in invoice documentation.

Subtask 4.1 – Deliver monthly Progress reports to TOCOR: Monthly progress reports will include a written monthly technical progress report that includes the following: (a) an overview of work accomplished since project inception; (b) a description of work accomplished during the reporting period; (c) a summary of QA/QC activities since project inception including a summary of corrective action taken; (d) a brief summary of anticipated work during the following period; (e) a summary and details of the costs incurred for each task during the quarter and cumulatively; and (f) total remaining budget.

Task 4 Deliverables

Written progress reports will be provided to TOCOR monthly including an update of the project milestones. (Subtask 4.1)

FEDERAL ADVISORY COMMITTEE ACT (FACA)

The Academy has developed policies and procedures to implement Section 15 of the Federal Advisory Committee Act, 5 U.S.C. App. Section 15 includes certain requirements regarding public access and conflicts of interest that are applicable to agreements under which the Academy, using a committee, provides advice or recommendations to a Federal agency. In accordance with its Congressional Charter and the requirements of Section 15, the Academy must provide independent, unbiased advice without actual or perceived interference or management of the outcome (findings and recommendations). Therefore, the Academy requires the right to publish all unclassified materials without any restriction over content and release, including any restriction that may require prior approval from the sponsoring agency.

In accordance with Section 15 of FACA, the Academy shall submit to the government sponsor(s) following delivery of each applicable report a certification that the policies and procedures of the Academy that implement Section 15 of FACA have been substantially complied with in the performance of the contract/grant/cooperative agreement with respect to the applicable report.

PUBLIC INFORMATION ABOUT PROJECTS

In order to afford the public greater knowledge of the National Academies activities and an opportunity to provide comments on those activities, the National Academies posts on its website (http://www.nationalacademies.org) the following information as appropriate under its procedures: (1) notices of meetings open to the public; (2) brief descriptions of projects; (3) committee appointments, if any (including biographies of committee members); (4) reports; and (5) any other pertinent information. Notices of public sessions at committee meetings are posted on the National Academies website at least 10 business days in advance. Anyone is free to attend. Public comments can be provided during public sessions.

ESTIMATE OF COSTS

The estimated cost for this study is $990,257 over a 24-month period. The period of performance is March 23, 2021 through March 21, 2023.

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